REMARKS

Claims 1, 7-11, and 17-19 are pending. The pending claims all feature a method of inhibiting angiogenesis. The method includes administering to a subject a syndecan-4 nucleic acid molecule that can bind to cellular syndecan-4 mRNA; a syndecan-4 nucleic acid complementary to the coding strand of a double stranded cDNA molecule; or an antibody that specifically binds to a syndecan-4 protein, where the agent decreases syndecan-4 expression, level, or activity, in the subject.

All of the pending claims are rejected under 35 U.S.C. 112, first paragraph, as lacking an enabling disclosure. The Examiner argues that the claimed methods are "unpredictable and unreliable." This rejection is respectfully traversed, for at least the following reasons.

The claims are enabled if one of ordinary skill in the art can make and use the claimed invention without undue experimentation. Applicants have prepared syndecan-4 null mice, and have quantified a difference in wound healing of the syndecan-4 null mice versus the syndecan-4 positive mice, demonstrating a significant delay in wound healing of the syndecan-4 null mice. Additionally, Applicants have demonstrated a statistically significant degree of impaired angiogenesis in syndecan-4 null mice (i.e., demonstrating a statistically significant reduction of the average vessel size in the granulation tissue of the syndecan-4 null mice). Accordingly, Applicants have provided proof *in vivo* that reducing syndecan-4 inhibits angiogenesis. Each of the Examiner's arguments and cited references are addressed in turn below.

In support of the rejection, the Examiner cites Mak *et al.* and Chang *et al.* to support the proposition that interpretation of data from knockout mice is "often unpredictable and unreliable." Essentially, the Examiner asserts that "the skilled artisan cannot predict with any certainty that the agents claimed would function in a manner similar to that exemplified by the syndecan-4 null mouse model." In support of this assertion, the Examiner cites Mak *et al.*, noting the following:

> (E)ngineered mutations in one gene can affect the expression of unaltered neighboring genes, giving rise to phenotypes that are unconnected to the gene of interest; and that gene deletions can also affect the architecture of an organ, such as the lymph nodes or

> spleen, which would have secondary effect on cells within these organs. Mak et al. conclude that there is a danger that such effects might be misinterpreted as primary effect of the gene mutation on the cells themselves. (See Office Action, page 3, second paragraph, emphasis added.)

Applicants have shown that mice lacking expression of the syndecan-4 gene experience delayed wound healing and reduced blood vessel formation. Although the Examiner has asserted that it would be difficult to predict whether the agents act in a direct or an indirect manner, the Examiner has provided no evidence that it would be difficult to predict whether the recited agents would actually inhibit angiogenesis as presently claimed. Applicants are claiming a method of inhibiting angiogenesis by administering an agent that reduces the expression, level or activity of syndecan-4. Whether the inhibition of angiogenesis is due directly to the reduction in syndecan-4 expression or activity (i.e., a primary effect) or whether the effects are due to the altered expression of a neighboring gene (i.e., a secondary effect) is irrelevant, as Applicants are not claiming the specific mechanism by which the angiogenesis is inhibited.

The Examiner further asserts that the expression pattern of a target does not necessarily predict its *in vivo* function. To support this proposition, the Examiner cites Chang, which discusses how the expression patterns of certain components of the TGF-β pathway do not predict their *in vivo* function. Applicant fails to see how this reference supports non-enablement of the present claims. The Examiner's reliance on Chang is misplaced as Applicant's data does not extrapolate from expression patterns (or any such *in vitro* data) to predict the *in vivo* effects of syndecan-4. Rather, Applicant have defined an *in vivo* function of syndecan-4 by performing *in vivo* experiments. I.e., Applicant's results from experiments in syndecan-4 knockout mice show that suppression of syndecan-4 reduces angiogenesis. If anything, Chang support the idea that experiments with knockout mice (as in the present application) can define the *in vivo* function of a given protein. Chang states:

> generation of mice lacking specific components of the TGF-β superfamily signal transduction cascade will remain an important approach to define the in vivo functions of these proteins. (Chang, page 44, emphasis added.)

In another aspect of the rejection, the Examiner asserts that "assuming that the efficacy of the agents claimed were predictable based on the results obtained from the transgenic mouse model, the art at the time of filing had not established with any certainty the predictability and feasibility of using the reducing agents in inhibiting angiogenesis in subjects." (See Office Action, page 4, lines 5-11.) In support of this assertion, the Examiner cites Kerbel R *et al.* (which discusses clinical applications of angiogenesis inhibitors) for the proposition that "there are many challenges and factors that must be determined before such treatment is effective." Applicants disagree that Kerbel supports non-enablement. Indeed, Kerbel notes that various angiogenesis inhibitors have been developed and that this approach is particularly promising. (See Kerbel, p. 727, col. 1, second paragraph.) Moreover, the Examiner's argument that "some drugs when administered can induce stable disease" supports enablement. Stable disease is a desirable outcome of angiogenesis therapy. Angiogenesis is the process of forming new blood vessels, which are required for a tumor to grow, because as the tumor becomes larger it requires a larger blood supply. Thus, an agent that successfully inhibits angiogenesis can induce stable disease, meaning that the agent can stop the tumor from growing further by preventing the formation of new blood vessels. Accordingly, successful angiogenesis therapy does not necessarily require tumor regression, but rather, successful angiogenic therapy in cancer may simply decrease the growth rate of a tumor (i.e., by slowing the rate of formation of new blood vessels).

Finally, the Examiner asserts that many challenges exist for the use of anti-angiogenesis treatment. However, this is true of many cancer treatments. For example, the Examiner cites "conflicting results of one particular gene therapy approach of the anti-angiogenesis drug endostatin" (where endostatin, when administered using expression of an adenovirus, was significantly less effective than when endostatin was administered via transfection into tumor cells that were then implanted into mice) in support of "the unpredictable nature of anti-angiogenic drugs." (See Office Action, page 5, first full paragraph.) However, the Examiner is taking this example out of context, overemphasizing one example that merely resulted in differing degrees of efficacy to suggest anti-angiogenic compounds are unpredictable as a whole.

Applicants assert that when balancing the one particular example cited by the Examiner against the list of 11 direct angiogenesis inhibitors provided in Table 1 (over half of which are currently in clinical trials) and the characterization of this class of compounds by Kerbel as particularly promising, one of skill in the art would find that the level of predictability of treatment with anti-angiogenesis agents is high.

Applicants have sufficiently enabled the invention if they have provided sufficient information to teach a person skilled in the art to make and use the invention without undue experimentation. This determination is made using the list of factors outlined in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In the case of the present invention 1) the claims are substantially narrowed to include specific agents including nucleotides and antibodies; 2) the state of the prior art is advanced, including many angiogenesis agents that are currently in clinical trials; 3) the level of ordinary skill in the art is high; 4) applicants have provided in vivo data; and 5) the specification provides significant guidance with regard to administration of the agents (See Specification, the paragraph bridging pages 29 and 30). A weighing of all the factors outlined in *In re Wands* supports a conclusion that the pending claims are enabled.

In view of the foregoing, Applicants assert that all of the presently pending claims are sufficiently enabled and requests that the corresponding rejection be withdrawn.

Enclosed is a Petition for Extension of Time. Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket number 10284-029001.

Respectfully submitted,

Date: November 24, 2003

Catherine M. McCarty Reg. No. 54,301
for: Louis Myers
Reg. No. 35,965

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906